REMARKS

This amendment is responsive to the Office Action mailed May 4, 2006. Withdrawn Claims 1-3 and 15-35 have been cancelled herein. Claims 4-14 are pending.

Claims 4-10 have been amended herein to specify using an agent that is a combination of (i) selenium or a selenium salt, and (ii) a retinoid. Support for the amendment can be found in former Claim 11, which is cancelled herein. Additional support can be found throughout the specification, *see, e.g.*, page 8, lines 4-19; page 20, lines 1-6; and the paragraph bridging pages 24 and 25 of the specification. No new matter is presented.

Claims 4-10 have additionally been amended to delete the recitation "at least partially", which recitation is objected to by the Examiner as indefinite.

Additionally, Claims 4, 5, and 10 have been amended to delete phrase "preventing" HCV infection.

Claim 12 has been amended to specify a selenium salt. Support for the amendment is apparent from the original claims.

Claim 13 has been amended herein to include reference to pegylated alpha interferon. Support for the amendment can be found on page 26, lines 12-18, and Example 15 of the specification.

Lastly, new dependent Claims 36-39 have been added. New Claim 36 specifies that the agent administered according to the invention further includes alpha interferon or pegylated interferon. Support for the amendment is apparent from original Claim 13 and page 26, lines 12-18, and Example 15 of the specification. New Claims 37-39 further specify that the agent further includes ribavirin. Support for new Claims 37-39 is apparent from original Claim 14.

No new matter is presented.

Response to issues presented under 35 U.S.C. §112, second paragraph

Claims 4-14 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner objects to Claims 4-10 because of the recitation "at least partially", which the Examiner considers a relative term.

As noted above, Applicants have amended Claims 4-10 to delete the objected to recitation "at least partially."

Applicants submit that the amendment obviates the rejection under 35 U.S.C. §112, second paragraph, and therefore withdrawal of the rejection is respectfully solicited.

Response to issues presented under 35 U.S.C. §112, first paragraph

Claims 4-8 and 10-14 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner states:

> "the specification, while being enabling for observation of low GI-PGx [sic] is correlated with low HCV RNA in a cell culture system, does not reasonably provide enablement for using any agent that can active [sic] the serum GI-PGx [sic] to prevent and treat HCV infection." (Office Action, page 3.)

Applicants note that the crux of the Examiner's concerns appear to be regarding the "prevention" of HCV, (*see, e.g.*, Office Action, paragraph 11) and the use of "any or such agents" to prevent HCV infection (*see, e.g.*, Office Action, paragraph 10). As noted above, Applicants have amended the claims herein to delete reference to "prevention" of HCV. Additionally, Applicants have amended all independent claims to recite specific compound agents to be used in the claimed methods. For example, Claim 4, as currently amended, recites:

> 4. (currently amended) A method for ~~preventing and/or~~ treating Hepatitis C virus infection and/or diseases associated with HCV infection in an individual comprising the step of administering a pharmaceutically effective amount of an agent which activates ~~at least partially~~ the activity of said human cellular protein gastrointestinal glutathione peroxidase or which activates or stimulates ~~at least partially~~ the production of said human cellular protein gastrointestinal glutathione peroxidase, wherein said agent is a combination of (i) selenium, or a selenium salt, and (ii) a retinoid selected from the group of: 9-cis retinoic acid, salts of 9-cis retinoic acid, C1 - C10 alkyl esters of 9-cis retinoic acid, salts of C1 - C10 alkyl esters of 9-cis retinoic acid, C1 - C10 alkyl amides of 9-cis retinoic acid, salts of C1 - C10 alkyl amides of 9-cis retinoic acid, 13-cis retinoic acid, salts of 13-cis retinoic acid, C1 - C10 alkyl esters of 13-cis retinoic acid, salts of C1 - C10 alkyl esters of 13-cis retinoic acid, C1 - C10 alkyl amides of 13-cis retinoic acid, salts of C1 - C10 alkyl amides of 13-cis retinoic acid, retinol, retinoic acid adlehyde, etretinate, N-(4-hydroxyphenyl) retinamide (4-HPR), 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (CD437; AHPN), all-trans-retinoic acid, C1 - C10 esters and amides of all-trans-retinoic acid, paraquat, 4-[E-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid, 4-hydroxyphenylretinamide, and 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)carboxamido]benzoic acid.

Applicants submit that the claim amendments proposed herein address the Examiner's enablement concerns. By following the descriptions and examples of the specification, a person skilled in the art can readily put the methods claimed into use and can readily determine the effectiveness of those methods in treating HCV. In view of this, it is submitted that the adequacy of the specification to enable the methods of the claims is clear, and the requirements of 35 U.S.C. §112, first paragraph, have been amply met.

Accordingly, in view of the amendments herein and the reasons set forth above, reconsideration and withdrawal of the rejection of Claims 4-8 and 10-14 under 35 U.S.C. §112, first paragraph, are respectfully solicited.

Response to issues presented under 35 U.S.C. §102

Look et al.

Claims 4-14 stand rejected under 35 U.S.C. §102(b) as being unpatentable over Look et al., *Antiviral Research*, 43:113-122 (1999) (hereinafter "Look"). Specifically, the Examiner contends that Look teaches:

> "administering IFN and or selenium to an HCV-infected individual. Look d al. [sic] disclose administering a combination therapy to patients infected with HCV wherein the combination comprises IFN and selenium." (Office Action, page 5.)

Look, in fact, teaches combining ***N*-acetylcysteine (NAC)** or glutathione (GSH) esters in combination with selenium as a combination therapy with IFN to treat patients suffering from HCV infection. Look explains:

> "Although not confirmed in all studies [internal cite omitted] hepatic and systemic levels of endogenous antioxidant (GSH), which may be reduced in chronic hepatitis C, were correlated with serum ALT activity, viral load and the grade of hepatic inflammation." (Look, page 114.)

Look then hypothesizes:

> "Since GSH itself is not transported over biomembranes and cannot be substituted directly, ***its repletion might be possible by providing precursors such as N-acetylcysteine (NAC)*** or GSH esters." (Look, paragraph bridging pages 114 and 115.)

Look then organized three groups of HCV patients and administered either IFN-therapy, IFN-therapy with NAC and sodium selenite, or IFN-therapy with NAC and sodium selenite plus vitamin E. Look observed the patient's clinical indications for 24 weeks and concluded:

> "In this controlled randomized pilot trial, **no significant overall advantage of antioxidant/IFN combination therapy** in terms of frequency of complete primary response after 6 months was found as compared to IFN monotherapy.
>
> ***
>
> However, the data suggest a potential beneficial effect for combining IFN treatment **with vitamin E supplementation**." (Look, paragraph bridging pages 119 and 120."

Applicants note that the claims, as amended, recite methods of treating HCV infection (and/or diseases associated therewith) by administering an agent comprising the combination of selenium or selenium salts and a retinoid.

A rejection for anticipation under 35 U.S.C. §102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference. *See* MPEP §2131. Since Look only discloses the use IFN-therapy with NAC and sodium selenite plus vitamin E and positively discloses that, in the absence of Vitamin E, the combination therapy appeared to be *ineffective* in their studies, Claims 4-14, which are directed the combination of selenium or selenium salts and a retinoid, cannot be said to be anticipated by Look as a matter of law. Reconsideration and withdrawal of the rejection under 35 U.S.C. §102 are requested.

Rumin et al.

Claims 9 and 11 stand rejected under 35 U.S.C. §102(b) as being unpatentable over international publication WO 99/67362 to Rumin et al. (hereinafter "Rumin"). Specifically, the Examiner contends that Rumin teaches: "administering selenium and/or retinoic acid to HCV infected cells." (Office Action, page 5.)

Foremost, it is noted that Rumin is directed to *in vitro* culture media to culture cell lines infected with HCV. There is no discussion of treatment of patients suffering from HCV infection or regulating the expression of the human cellular protein gastrointestinal glutathione peroxidase. Rather, Rumin is directed to propagating a cell line infected with HCV in a culture medium containing mammalian plasma or sera; a chemical or biological compound giving an antioxydative property and/or differentiating property, such as dimethyl sulfoxide (DMSO), retinoic acid, a vitamin, for example vitamin E, or

selenium; and a corticoid.

Moreover, Applicants note that Rumin actually fails to provide a single example of a culture medium including retinoic acid, a vitamin, or selenium in any practical example. Applicants note that only dimethyl sulfoxide (DMSO) and a corticoid are taught. *See, e.g.*, Example 1 of the description.

A rejection for anticipation under 35 U.S.C. §102 requires that each and every limitation of the claimed invention be disclosed in a single prior art reference. *See* MPEP §2131. However, in order to qualify as prior art under §102(b), the allegedly anticipatory art must have an enabling disclosure. MPEP §2121.01. A reference contains an enabling disclosure if the public was in possession of the claimed invention before the date of invention. MPEP §2121.01.

Importantly, an allegedly anticipatory reference is *not* enabling if it does not teach a person skilled in the art to make/use the invention without an undue amount of experimentation. *Helifix v. Blok-Lok*, 208 F.3d 1339, 53 USPQ2d 1299 (Fed. Cir. 2000), citing *In re Sheppard*, 339 F.2d 238, 242, 144 USPQ 42, 45 (CCPA 1981).

Applicants submit that Rumin is wholly irrelevant to the present invention and at best fails to provide any enabling teachings relating to co-administration of selenium and retinoids.

Furthermore, even if the Rumin reference were enabling for use of selenium or retinoids, which Applicants submit is not the case, the reference would still fail to anticipate the claims as amended. Applicants' claims, as amended, recite methods of treating HCV infection (and/or diseases associated therewith) by administering an agent comprising the combination of selenium or selenium salts **and** a retinoid.

Rumin, at best, suggests utilizing **a** chemical or biological compound "having antioxydative property and/or differentiation property, such as DMSO, retinoic acid, vitamin, for example vitamin E, or selenium" in a culture medium for the successful propagation of cell lines infected with HCV. There is absolutely no teaching or suggestion of combining both a selenium salt and a retinoid for any purpose whatsoever, let alone for treating HCV.

Accordingly, Claim 9, which is directed regulating the expression of GI-GPx utilizing the combination of selenium or selenium salts **and** a retinoid, cannot be said to be anticipated by Rumin as a matter of law. Claim 11 has been cancelled herein. Reconsideration and withdrawal of the rejection under 35 U.S.C. §102 are requested.

Respectfully submitted,

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November 6, 2006
date

Melanie McFadden